REMARKS

Claims 2-5 and 8-16 are currently pending in the application. Claims 3-5 and 8-14 are withdrawn from consideration and are herein canceled. Applicants also cancel claim 16 without prejudice. Claim 15 is in independent form.

Applicants wish to express their appreciation for the courtesies extended Applicants' representative, Laura S. Dellal, during a personal interview conducted on March 12, 2008, with the Examiner's supervisor, Examiner Jon P. Weber.

I. Applicants have overcome the rejection of claims 2, 15, and 16 under 35 U.S.C. §112, first paragraph.

Claims 2, 15, and 16 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement because of limitations that are new concepts because they do not have literal support in the as-filed specification by way of generic disclosure, nor are there specific examples. Specifically, the Office Action holds that the limitation "the products consisting essentially of the secretions from the mesenchymal stem cells" in the active step of administering stem cell products in the method of improving cardiac function has no support in the as-filed specification. The active step of "separating the mesenchymal stem cells from a supernatant, the supernatant containing products consisting essentially of secretions from the mesenchymal stem cells" and "improving cardiac function" as a result of administering the "products consisting essentially of the secretions from the mesenchymal stem cells" in the method of improving cardiac function has no support in the as-filed specification. The Office Action holds that the generic disclosure relates to the potential benefits of the stem cells in combinations with their secretions but not to the secretions alone as a sole therapeutic agent. The Office

Action further holds that the specification defines the term "stem cells" as cells having the ability to give rise to the hematopoietic lineage cells and thus the generic term "stem cells" is used in the specification for the hematopoietic stem cells rather than for mesenchymal stem cells. Consequently, the generic stem cell products would be understood as hematopoietic stem cell products. The Office Action further indicates that removal of the "new matter" will result in the reinstatement of the rejection of claims 2, 15, and 16 under 35 U.S.C. §102(b) based on Pierpaoli, et al. Reconsideration of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim 15 has been amended to more clearly define the invention. The terms discussed by the Office Action have been removed, without prejudice, rendering this rejection moot.

Support for the amendment to claim 15 can be found in Example 3, pages 22 – 25. Hypoxia (HX) "was produced by placing BMSC in an airtight incubator where room air was replaced by 95%N_2/5%CO_2. BMSC incubated under normoxic (95%Air/5%CO_2) condition (NX) served as a control. BMSC were harvested after one hour of exposure to HX or NX. The *media left after harvesting of BMSC* was used for another set of experiments" (p. 23 of Specification, lines 2-7, emphasis added). Furthermore, "culturing of BMSC in HX preconditioned media also increased the expression of HIF-1α ... and ... Stat-3" and "in the media, expression of HIF-1α was significantly higher after one hour of exposure to HX compared to NX" (p. 23, lines 21-23 and 26-28). Also, "based upon the above findings, it can be concluded that hypoxia preconditioned BMSC media represents a potential drug for treatment of the failing heart..." (p. 25, lines 19-21).

With respect to the statement by the Office Action that the removal of the "new matter" will result in the reinstatement of the rejection of claims 2, 15, and 16 under 35

U.S.C. §102(b) based on Pierpaoli, et al., Applicants point out that the present invention as currently claimed is not anticipated by Pierpaoli, et al.

Pierpaoli, et al. specifically states that "an ultrafiltration fraction of MW > 100,000 *separated from the original medium in which the bone marrow had been suspended (supernatant)*" was designated marrow regulating factors (MRF) and administered to mice. Abstract, emphasis added. Pierpaoli, et al. cannot anticipate the present invention because the supernatant containing stem cell products is not administered as required in the presently amended claims, only one specific fraction with a molecular weight of over 100,000 *without the supernatant*. The supernatant, i.e. preconditioned media, is not used at all in Pierpaoli, et al. Further, there is no disclosure in Pierpaoli, et al. of the required step of improving cardiac function. Thus, with the current amendments to the claims, the present invention is patentable over Pierpaoli, et al.

As each step of the claims is fully supported by the specification and the Office Action's specific issues with the language of the claims have been addressed herein, reconsideration of the rejection under 35 U.S.C. §112 to claims 2, 15, and 16 is respectfully requested.

II. Applicants have overcome the rejection of claims 2, 15, and 16 under 35 U.S.C. §102(e).

Claims 2, 15, and 16 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,368,636 to McIntosh, et al. (hereinafter the '636 patent). Specifically, the Office Action holds that the '636 patent discloses a method for reducing transplant rejection including heart transplant by reducing immune response as a result of administering MSC supernatants. The MSCs are isolated form bone marrow, expanded in culture, and used for making the MSC supernatants. The MSCs are cultured under 5% carbon dioxide and 95% air and thus, in the atmosphere with reduced oxygen amounts or under hypoxia.

Reconsideration of the rejection under 35 U.S.C. § 102(e), as anticipated by the '636 patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

The present invention, in contradistinction, requires hypoxic conditions of 95%N_2/5%CO_2, which is much different than the conditions of the '636 patent. The conditions of the '636 patent are considered "normoxic" conditions according to the present invention. Evidence is presented in Example 3 of the present invention that "hypoxic" and "normoxic" conditions produce different results when the BMSC are exposed to each condition.

Since the '636 patent does not disclose hypoxic conditions of 95%N_2/5%CO_2, the present invention is patentable over the '636 patent.

III. Applicants have overcome the rejection of claims 2, 15, and 16 under 35 U.S.C. §103(a).

Claims 2, 15, and 16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 7,097,832 to Kornowski, et al (hereinafter the '832 patent) in view of U.S. Patent No. 6,368,636 to McIntosh, et al. Specifically, the Office Action holds that the '832 patent discloses and/or suggests a method of improving cardiac function wherein the method comprises steps of culturing bone marrow stem cells under hypoxia conditions for enrichment in the secretions from the stem cells and administering bone marrow stem cells and the bone marrow secretion products. The '832 patent discloses that the bone marrow secreted factors are necessary to promote new blood vessel growth and to restore function of ischemic heart and it also suggests administration of the bone marrow cell secretions. The Office Action holds that the '636 patent discloses the additional beneficial effects of the

MSC supernatants such as reduction of transplant rejection including heart transplants and thus teaches and/or suggests reducing immune response by administering the MSC supernatants during heart transplantations and improving cardiac function within the broadest meaning of the instant claims. Therefore, the Office Action holds that it would have been obvious to administer the bone marrow stem cell secretions to the ischemic heart with a reasonable expectation of success as well as administer the MSC supernatants to reduced immune response during heart transplantation to improve cardiac function. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the '832 patent is respectfully requested.

The '832 patent discloses a method of treating cardiac or myocardial conditions by administering autologous bone marrow. The marrow can be exposed to hypoxia to activate the transcription factor HIF-1. The marrow is injected into a patient and there it secretes angiogenic factors. There is no disclosure or suggestion of performing the method disclosed by Applicants in presently pending independent claim 15. It is already known in the art, as Applicants explain in the background section of the specification, that marrow itself can be injected into the myocardium and stromal cells in the marrow can show growth potential. Furthermore, as stated above, the '636 patent does not disclose a preconditioned media being exposed to hypoxic conditions of 95%N_2/5%CO_2. Thus, there is no showing of a hypoxic BMSC preconditioned media being administered alone that can improve cardiac function as required by the steps of claim 15.

Since neither the '832 patent alone or in combination with the '636 patent or with knowledge in the art suggests the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

It is respectfully requested that the present amendment be entered in order to place the application in condition for allowance or at least in better condition for appeal. The application is placed in condition for allowance as it addresses and resolves each and every issue that remains pending. Claims have been amended to clearly distinguish over the prior art while raising no new issues that would require further searching. Hence, it is respectfully requested that the amendment be entered.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Terry Horst